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EXAMINER	
EISENSCHENK,F	
ART UNIT	PAPER NUMBER
1816	22

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9/28/96 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-40 are pending in the application.
   Of the above, claims 21-27, 30, 31, 35 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-20, 28, 29, 32-34, 36-40 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Claims currently under consideration are 1-20, 28-29, 32, 33, 34, and 36-40. Claims 21-27, 30-31, and 35 stand withdrawn from consideration. Applicants' request to hold the drawing requirements in abeyance until such time as allowable subject matter is identified is noted. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior office action. The location of this application has changed. All future correspondence regarding this application should be sent to the Examiner's attention with art unit designation 1816. Current fax and telephone contact numbers may be found at the end of this Office Action.

2. The interview of 10/8/97 is noted. In the interview, the Examiner indicated that a prior art search for T-cells transfected with DNA would be performed to provide motivation to transfect T-cells with antibody-polycation-DNA constructs. However, such a reference is already of record in the Hirsch patent. Applicants' comments regarding In re Payne were noted. Case law with more relevance to the substitution of equivalents/obviousness issue has been provided below. Applicants' comments regarding the selection of T-cell antibodies as targeting agents out of the genus of all antibodies is noted, but given the teachings of Hirsch et al. wherein such antibodies are used to transfect T-cells, the comments have not been found persuasive given that the person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986). This relevant prior art relates to those persons engaged in transfection of T-cells with antibody-polycation-DNA constructs.

3. Claims 1-8, 11-20, and 36-40 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. or Hirsch et al. ('132), Carriere et al., Knapp et al., and Young et al. (J. Immunol., 136:4700) or Weinberger et al. (J. Cell. Biochem.). Claims 1-5, 7-8, and 11-16 are drawn to protein-polycation conjugates wherein the targeting component of the conjugate is a T-cell specific monoclonal antibody or a protein that specifically binds to a T-cell antigen such as CD4 (i.e. the HIV protein gp120). The claims are also drawn to the use of modified histones, histones, polylysine, protamine in the conjugates as the polycation substance. Claims 17-20 are directed to complexes comprising the conjugates of claim 1 with associated nucleic acids. Claims 36-37 are drawn to a process for the introduction of nucleic acids into T-cells through the use of the conjugates of claim 1. Wu et al. teach a method of transfecting hepatocytes using asialoproteins conjugated to polycations for the transfection of liver cells (see abstract and column 4, paragraph 2). Wagner et al. teach the use of transferrin-polycation conjugates for the transfection of cells with DNA including the use of polylysine and protamine. Wu et al. teach a number of polycationic molecules useful in the instant invention, including histones, polylysine, etc (column 4, paragraph 2). Wu et al. teach that other targeting agents (i.e. hormones or antibodies) may be used to direct the

conjugates to the target cell (see columns 5-6, The nature of the Ligand) and that agent used will depend upon the target cell. The references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells.

Goers et al. teach that therapeutic agents are selected for their intended application. Where the targeting of therapeutic agents to T-cells is contemplated, antibodies specific for T-cell antigens would be selected.

Furthermore, Hirsch et al. teach the T-cell specific antibody-DNA conjugates and the use of T-cell specific antibodies to target nucleic acids to T-cells for transformation purposes or in order to produce interleukins, etc. (see Example 3).

Carriere teaches that anti-CD4, CD7, and CD5 antibody conjugates are internalized by cells expressing these cell markers (see Abstract and Discussion). CD7 is an admitted tumor associated antigen (see specification, pages 12-13). The substitution of such antibodies as targeting agents of protein-polycation complexes would have ben obvious to one of ordinary skill where the targeting of T-cell was desired. Such targeting would be desired when one wished to treat T-cell leukemias or HIV infected T-cells or to induce the production of lymphokines (see Hirsch). The use of gp120 to target polycation-nucleic acid complexes to CD4 expressing cells would be functionally analogous to using anti-CD4 antibodies, and in view of the state of the art at the time of invention, an obvious means of targeting therapeutic agents to CD4 expressing cells in view of the state of the art and the recognition in the art that the HIV virus was internalized into CD4 expressing cells through the interaction of gp120 with the CD4 molecule. Zon et al is found at page 18 of the specification and is referred to therein as representing known methods of making nucleic acid analogues. This reference also teaches that such analogues are useful for the treatment of HIV infection. Applicants' comments regarding the Carrier (sic) reference are noted. The reference was cited for its teaching that anti-CD4, anti-CD7, and anti-CD5 antibodies were internalized into cells. That the antibodies were bound to gold is immaterial to the issue at hand, however it does provide for teaching that antibody conjugates wherein anti-CD4, anti-CD7, and anti-CD5 antibodies were used as the targeting agents were internalized into cells.

Young et al. and Weinberger et al. teach that T-cells transfected with gamma interferon or differentiation antigen encoding DNA express the interferon or differentiation antigen. Thus, one skilled in the art would have had a reasonable expectation of success in expression of genes transfected into T-cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids

because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for the purpose of introducing foreign DNA into the cells for either therapeutic purposes or for the production of interleukins (as is indicated by the Hirsch reference). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

4. **RESPONSE TO TRAVERSAL:** Applicants' arguments have been considered but are not found persuasive for the following reasons and those set forth in the previous Office Action (see paper #18). Applicant has argues that the rejection oversimplifies the issue. Applicant is respectfully reminded of the test for obviousness. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

Scope and Content of the Prior Art: The conjugates of transferrin, polycations, and attached DNA were known before the filing date of the present invention. These conjugates were known to form soluble complexes with DNA and be "adsorbed" into cells (see Wu et al. or Wagner et al.) Applicant is invited to consider paragraph 1, column 2, Wu et al. where it is explicitly taught that the invention is directed to the use of receptor mediated endocytosis to endow cell specificity to gene delivery. The Wu invention uses a ligand-polycation-DNA complex to achieve such delivery. Wu teaches that antibodies may be the targeting ligand within the taught invention. Wagner teach the use of transferrin-polycation-DNA complexes to transfect cells, and while limited to "transferrinfection" teaches that protein-polycation-DNA complexes were useful for the delivery of DNA into cells.

Hirsch explicitly teaches (see column 3) the use of antibody-DNA conjugates for the transfection of T-cells (wherein the antibodies are T-cell specific, i.e. CD3 specific). The use of antibodies to deliver DNA and toxin or DNA into cells was well established at the time the invention was filed, see Goers et al. Young teaches that T-cells transfected with DNA expressed the protein encoded by the DNA.

Carriere taught that anti-CD4, anti-CD7, and anti-CD5 antibodies were internalized into cells. At issue is whether the routineer would have recognized that another "targeting" agent, such as an antibody known to be internalized into cells,

would have been useful for the direction of DNA into cells and whether such a routineer would have been motivated to substitute such an antibody for the transferrin molecules of the prior art. The primary references differ from the claimed invention in only the targeting agent used to direct the DNA into a cell. One of ordinary skill in the art would have recognized that a molecule which caused internalization of a bound ligand would have been useful as a targeting component of a conjugate comprising a protein-polycation conjugate which are capable of forming soluble complexes with nucleic acids and which are also adsorbed into cells.

Thus, the scope and content of the prior art indicate that the art recognized that T-cell specific antibody-DNA constructs were useful for the transfection of T-cells, that transfected T-cells expressed the genes with which the cells were transfected, and that antibodies could be used as the targeting ligands in the system of Wu et al. The art also recognized other antibodies which were internalized by T-cells (Carriere et al.). The differences between the prior art and the claimed invention involve the use of T-cell specific antibodies in the place of the generically taught antibodies of the Wu patent. The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986). In determining this skill level, various factors are considered, including "type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." Id. In a given case, every factor may not be present, and one or more factors may predominate. Id. at 962-63, 1 USPQ2d at 1201. The relative level of skill in the biotechnology arts is generally recognized to be high as is the sophistication of the technology. In the case of this invention, the routineer may be considered to be a Ph.D. or an M.D. with a number of years of post-doctoral experience who practices in the DNA art as relates to the transfection of cells with targeting constructs. One of ordinary skill in the art, with such a degree of education and expertise within the art would have recognized the equivalence of antibodies and transferrin as targeting ligands in the context of this invention.

As the CCPA stated in the decision In re RUFF AND DUKESHIRE, 118 USPQ 340 (CCPA 1958), mere substitution of an equivalent is not invention. The Court also stated that claims should not be rejected solely on applicant's own showing of equivalency; it is only where equivalency is known to prior art or obvious to one of ordinary skill in the art that substitution of one equivalent for another is not invention. Under the facts of the current situation, transferrin-DNA, anti-CD3-DNA conjugates (Hirsch et al.), anti-CD4, anti-CD7, and anti-CD5 antibodies were recognized to be internalized into cells. Wu explicitly teaches that antibodies may be used as targeting ligands in the system of the '320 patent. One of ordinary skill in the art would have recognized that transferrin and specific antibody were equivalents for the purposes of targeting DNA to cells, especially in view of the teachings of Wu which indicated that antibodies may be used as targeting agents in the place of transferrin. Thus, one of

ordinary skill in the art would have been motivated to use such targeting agents (i.e. antibodies) to deliver nucleotides into cells where such targeting agents were a component of a protein-polynucleotide conjugate capable of forming soluble complexes with DNA and being internalized into cells, especially in view of the teachings of Wu et al. which indicated that transferrin and antibodies were suitable targeting vehicles for the introduction of DNA laden polycation complexes.

5. Claims 17, 20, 28-29 and 32-34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al., Hirsch et al. ('132), Knapp et al., and Carriere et al., as applied above and further in view of Haseloff et al., or Rossi et al. ('019) and Applicants' admitted prior art regarding oncogene inhibitory nucleic acids (see page 26, paragraph 3 of the specification). The teachings of the Wu et al. (AC1), Wagner et al. (AT2), Goers et al., and Hirsch et al. ('132) references have been discussed above. Claims 28-29 and 33-34 are drawn to protein-polycation/nucleic acid complexes wherein the nucleic acid is a ribozyme which an inhibitory nucleic acid or an oncogene inhibitory nucleic acid and the targeting component of the conjugate is a T-cell specific monoclonal antibody or a protein that specifically binds to a T-cell antigen such as CD4 (i.e. the HIV protein gp120). Wu and Wagner differ from the claimed invention in that the use of antibody targeting agents and nucleic acids comprising ribozymes are not taught. Therapeutic agents of the gene therapy category also include ribozymes. Haseloff et al. teach ribozyme enzymes (ribozymes) and a variety of applications for these molecules (see pages 590-591) such as the specific targeting of a particular gene RNA transcript with ribozymes. The "anti-gene activity" of ribozymes is indicated to provide a basis for gene therapy of various diseases, including HIV infection (column 1, '019). This section also indicates that transfection or transformation techniques to introduce genes encoding ribozymes into various types of cells were known in the art in 1988. Those skilled in the art would have been able to insert ribozymes into a variety of genetic constructs in order to facilitate the expression of the ribozyme of a desired specificity. Rossi et al. teach ribozymes capable of cleaving HIV-1 RNA and provide a variety of therapeutic applications for the disclosed ribozymes of their invention. Included in this teaching is that therapeutic ribozymes may be introduced into cells by a variety of methods including the transfection of cells with DNA encoding the ribozymes of a desired specificity (see column 6, Therapeutic Procedures). Ribozymes are also taught to be capable of inactivating endogenous RNA transcripts including those produced by the ras, myc, or src oncogenes. Ribozyme contained within tRNA transcripts are known in the art (see specification, page 19). In view of the teachings of Rossi et al. and/or Haseloff et al., one of ordinary skill would have recognized that the targeting of ribozymes to T-cells expressing oncogene proteins or HIV proteins using polycation-protein conjugates such as those taught by Wagner et al. would have been useful for inactivation of the genetic transcripts contained within the cells. Further, one of ordinary skill would have recognized, prior to Applicant's earliest priority date, that

the targeting specificity of the system disclosed by Wagner et al. could be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of ribozyme laden conjugates to T-cells for the purpose of introducing foreign nucleic acids, such as ribozymes, into the cells for the inactivation of RNA contained with the cells. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. **RESPONSE TO TRAVERSAL:** Applicants' arguments have been considered but are not found persuasive for the following reasons, those set forth in paragraph 17 herein, and those set forth in the previous Office Action (see paper #18). Applicants' traversal covers, essentially, the same ground as that in the previous traversal on the first 103 rejection set forth by the Examiner. Applicants' arguments have been considered but are not found persuasive for the following reasons: This invention substitutes antibodies which are internalized into cells for the transferrin molecule of the prior art as the means for the targeting of nucleic acids into cells. Applicant argues that there is no motivation to target ribozymes to T-cells based on the combination of references. The obviousness of the targeting agent-polycation conjugates have been discussed above. This rejection is based upon the additional element of ribozymes being recited in the claims. Ribozymes are a nucleic acid and one skilled in the art would have expected such ribozymes to be capable of association with the polycation-targeting agent conjugates produced in the previous rejection through the combination of references. One of ordinary skill in the art would have had a reasonable expectation of success in forming a protein (antibody)-polycation-ribozyme complex in view of the combination of references.

NEW GROUNDS OF REJECTION

7. Claims 1 and 9-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al. and Calliere et al., as applied above (see paragraph 18) and further in view of Goding et al., Ghetie et al. (Mol. Immunol., 23:1371), Ghetie et al. (Mol. Immunol., 25:473), or Mota et al. (Immunol. Letters). Claims 1 and 9-10 are drawn to compositions

comprising antibodies bound to polycations through protein A antibody interactions. The teachings of the references have been discussed in paragraph 18 and differ from the claimed invention in that the binding attachment of polycation to antibody through a protein A-antibody interaction is not taught in the combination of references. Goding et al. teach that protein A may be used as an immunological reagent for the attachment of reagents to antibody molecules. Specifically, the attachment of labels such as fluorescein or radioisotopes to cell bound antibodies is taught by the reference (see page 248). In view of the art recognition that labels such as fluorescein or radioisotope could be, and were, attached to antibodies through a protein A-antibody interaction, it would have been obvious to one of ordinary skill in the art that polycations could also be attached to antibodies through the protein A-antibody interaction, thereby providing a means of attaching DNA to antibodies or facilitate the isolation of antibodies through ion exchange chromatography. The Ghetie references and Mota et al. teach that those skilled in the antibody conjugate arts recognizes the usefulness of Protein A conjugates as "universal" agents which may then be conveniently attached to antibodies of any specificity, see Ghetie, Mol. Immunol., 23:1373.

One of ordinary skill in the art at the time the invention was made would have been motivated to select make an antibody-protein A-polycation compound because such proteins would have allowed for the specific direction and introduction of nucleic acid laden conjugates to T-cells or facilitated the isolation of such antibodies through ion exchange chromatography. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Applicant traverses on the grounds that the Examiner has utilized improper hindsight to reject the claims. The arguments has not been found persuasive for the reasons cited above and because one of ordinary skill in the art would have recognized that Protein A-polycation conjugates would have been an "universal" reagent useful for the attachment of DNA to IgG antibodies of any specificity. Indeed the art, in addition to Goding et al., had used such conjugates for the delivery of toxins to cells (see Ghetie et al. or Mora et al.). Applicants' arguments have not been found persuasive.

9. No claim is allowed.

10. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Eisenschenk whose telephone number is (703) 308-0452. The examiner can normally be reached Monday through Thursday from 6:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. The fax phone number for Group 180 is (703) 305-3014 or (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

CEisenschenk

October 24, 1997
Christopher Eisenschenk, Ph.D.
Primary Examiner
Group 1800